Dairy food products: good or bad for cardiometabolic disease?

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Abstract

Prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasingly and is a key risk for CVD development, now recognised as the leading cause of death globally. Dietary strategies to reduce CVD development include reduction of saturated fat intake. Milk and dairy products are the largest contributors to dietary saturated fats in the UK and reduced consumption is often recommended as a strategy for risk reduction. However, overall evidence from prospective cohort studies does not confirm a detrimental association between dairy product consumption and CVD risk. The present review critically evaluates the current evidence on the association between milk and dairy products and risk of CVD, T2DM and the metabolic syndrome (collectively, cardiometabolic disease). The effects of total and individual dairy foods on cardiometabolic risk factors and new information on the effects of the food matrix on reducing fat digestion are also reviewed. It is concluded that a policy to lower SFA intake by reducing dairy food consumption to reduce cardiometabolic disease risk is likely to have limited or possibly negative effects. There remain many uncertainties, including differential effects of different dairy products and those of differing fat content. Focused and suitably designed and powered studies are needed to provide clearer evidence not only of the mechanisms involved, but how they may be beneficially influenced during milk production and processing.

Key words: **Dairy foods: CVD: Type 2 diabetes: Vascular function**

Introduction

Cardiovascular (heart and circulatory) diseases cause more than a quarter of all deaths in the UK, or about 155 000 deaths per year with about 41 000 of these in individuals under the age of 75 years[1] and are the largest cause of death globally with 17·5 million deaths in 2012[2]. The cost to the UK of premature death, lost productivity, hospital treatment and prescriptions as a result of CVD is estimated at £19 billion each year. In addition there are now some 3·9 million individuals in the UK living with diabetes (90 % type 2) with about 700 cases being diagnosed every day. Projections indicate that there will be over 5 million cases by 2025. The annual total cost (direct and indirect) of diabetes in the UK is currently about £23·7 billion which is projected to increase to £38·9 billion by 2035[3]. The prevalence of diabetes (mostly type 2) worldwide has almost quadrupled since 1980 to 422 million adults, with deaths directly attributable to diabetes being 1·5 million in 2012[2].

CVD is a group of diseases of the heart and blood vessels and includes CHD, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolisms, heart attack and stroke[2]. There are a number of risk factors associated with the development of CVD, some of which are modifiable such as cigarette smoking, physical inactivity, high blood pressure, elevated total and LDL-cholesterol, reduced HDL-cholesterol, elevated TAG and being overweight. Out of these risk factors, hypertension poses the greatest risk for the development of CHD and particularly stroke, and causes 7·5 million deaths worldwide annually. However, recent data have revealed that dietary risks now account for the greatest loss of global disability-adjusted life years (DALY) for disease risk factors in 2013, overtaking smoking and hypertension[4]. The lost DALY are predominantly from CVD and diabetes (collectively along with the metabolic syndrome (MetS) now often termed cardiometabolic disease) and this presents a key challenge to nutrition scientists to identify effective dietary strategies and foods that can reduce disease risk and are acceptable and palatable to the population. A high intake of SFA and *trans*-fatty acids (TFA) has been linked to an increased risk of CVD, and this effect is thought to be mediated predominately by increased plasma LDL-cholesterol levels[5]. The UK and WHO dietary guidelines recommend <10 % of total

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energy intake from SFA, yet the majority of countries worldwide currently exceed this recommendation[6], with data from the most recent UK National Diet and Nutrition Survey (NDNS) reporting mean population SFA intakes of 12·0 % of total energy intake[7]. Milk and dairy foods (including butter) are the single greatest contributor to dietary SFA within the UK diet contributing 27 % to the adult diet and are also a source of ruminant TFA[7]. Elimination or reduction of their intake has been suggested as a strategy for CVD risk reduction; however, evidence from prospective cohort studies and randomly controlled dietary interventions studies does not support this, showing that consumption of milk and dairy products, except butter, is not consistently associated with an increased risk of CVD. The present review will examine the association between dairy products and cardiometabolic disease events derived from long-term prospective studies and the effect of milk and dairy foods on markers of cardiometabolic disease risk measured in human randomised controlled trials (RCT). Whilst the review will focus on adults, some of the key issues are also relevant to children. For example, it is notable that in the UK, children consume more SFA as percentage of total energy than adults, and in young children (aged 4–10 years) a greater proportion is supplied by dairy products (about 31 %) than in adults (about 22 %)[7].

Effect of milk and dairy products on risk of CVD

The chronic effects of milk and dairy products on health would best be examined in adequately powered RCT that use disease/death events as the key outcomes. To date, no studies of this design have been reported and it is unlikely that such studies will ever be performed in the future due to the high associated financial costs, ethical considerations and long study duration. Therefore, the most suitable evidence available on the associations between milk and dairy products on chronic diseases and survival is provided by long-term prospective cohort studies.

Milk and total dairy product intake and CVD risk: evidence from prospective studies

Over the past 20 years, a number of prospective cohort studies from various parts of the world have examined the relationship between milk and dairy product consumption and the risk of CVD and stroke. The results from the studies either showed no relationship[8–23] or an inverse association[24–29] between dairy product intake and risk of CVD and stroke.

A number of recent reviews have looked specifically at the association between milk and dairy food consumption and CVD, some of which have conducted meta-analyses of available cohort data (Table 1). Elwood et al.[30] reported on meta-analyses that examined the associations between milk and dairy products and health and survival. The Cochrane systematic review method was used and yielded eleven papers for CHD and four papers for stroke and diabetes. The authors concluded that the available data indicated a possible beneficial effect of milk and dairy product consumption on risk of CVD[30]. The relative risk (RR) of stroke and IHD in subjects

with high milk and dairy product intake was 0·79 (95 % CI 0·75, 0·82) and 0·84 (95 % CI 0·76, 0·93), respectively, relative to those with low milk and dairy product intake. This study has been extended to examine the differential effects of milk, cheese and butter on the incidence of vascular disease[31]. The authors reported a reduction in RR in the subjects with the highest dairy product consumption relative to those with the lowest intake: 0·87 (95 % CI 0·77, 0·98) for all-cause deaths, 0·92 (95 % CI 0·80, 0·99) for IHD, 0·79 (95 % CI 0·68, 0·91) for stroke and 0·85 (95 % CI 0·75, 0·96) for incident diabetes[31]. In a meta-analysis of seventeen prospective studies Soedamah-Muthu et al.[32] found a weak and marginally significant inverse association between milk intake and total CVD, but no significant association was seen with risk of stroke or CHD although in other meta-analyses significant inverse relationships were seen for stroke[33] and CVD/stroke/CHD[34]. The study of Qin et al.[34] which included a total of twenty-two prospective cohort studies reported RR 0·88 (nine studies; 95 % CI 0·81, 0·96) for CVD and RR 0·87 (twelve studies; 95 % CI 0·77, 0·99) for stroke. No association was found between dairy product consumption and CHD risk, which supports previous findings from Soedamah-Muthu et al.[35].

Recent studies that were not included in all these meta-analyses, such as The Netherlands Cohort Study consisting of 120 852 men and women with 10 years of follow-up, showed no association between total milk and milk product intake and stroke mortality in men and women[21]. Similarly, no association between total milk intake and IHD mortality in men was found, whereas in women, there was a weak but significant positive association (RR 1·07; 95 % CI 1·01, 1·13; P for trend = 0·05). Similarly, in the Rotterdam Study of older Dutch subjects[36], total dairy product consumption or the intake of specific dairy products was not related to CVD events. There was, however, an inverse association between high-fat dairy and fatal stroke (hazard ratio (HR) of 0·88 per 100 g/d; 95 % CI 0·79, 0·99), but not to incident stroke[36]. The findings of these studies appear to be in broad agreement with the meta-analysis findings of Soedamah-Muthu et al.[32].

Contrary to these findings, a study by Michaëlsson et al.[37] reported that milk intake was significantly associated with markedly higher total and CVD mortality in 61 433 Swedish women from the Swedish Mammography Cohort. This relationship was also observed in a cohort of 45 339 Swedish men, although the relationship was considerably weaker[37]. However, when these data were re-examined, an inverse association was observed for the number of CVD deaths against milk consumption[38] and, moreover, in a subset of 33 636 women also from the Swedish Mammography Cohort, Patterson et al.[39] reported that total dairy food intake was inversely associated with myocardial infarction (MI) risk (multivariable adjusted HR 0·77; 95 % CI 0·63, 0·95) and milk intake was not significantly associated with MI risk. The inconsistent findings between milk intake and CVD mortality observed within the same cohort require further investigation. A recent meta-analysis by Qin et al.[34], which included a total of twenty-two prospective cohort studies, showed an inverse association between dairy product consumption and overall risk of CVD (nine studies; RR 0·88; 95 % CI 0·81, 0·96) and stroke (twelve studies; RR 0·87; 95 % CI 0·77, 0·99). However, no association was

Table 1. A selection of recent reviews and meta-analyses on milk and milk products or total dairy product intake and risk of CVD

Reference	Dairy food	Methodology	Overall CVD	Stroke	CHD	IHD
Qin et al. (2015)[34]	'Dairy products' as the main exposure to represent milk and dairy products	Meta-analysis of 22 prospective studies	Inverse association of dairy products and overall risk of CVD (nine studies; RR 0·88; 95 % CI 0·81, 0·96)	Inverse association for stroke (12 studies; RR 0·87; 95 % CI 0·77, 0·99). RR reduced in low-fat dairy products	No association (12 studies; RR 0·94; 95 % CI 0·82, 1·07)	
Hjerpsted & Tholstrup (2016)[43]	Cheese	Narrative review of three correlation, five cross-sectional, five case–control, eight prospective and four RCT cross-over studies	Of eight prospective studies, four found no association of cheese intake and CVD, one an increased risk, two a decreased risk and one no association in men but a decreased risk in women			
Hu et al. (2014)[33]	Total dairy products and subtypes	Meta-analysis of 15 prospective studies, 28 138 stroke events from 764 635 subjects		Total dairy RR 0·88 (95 % CI 0·82, 0·94); low-fat dairy RR 0·91 (95 % CI 0·85, 0·97); fermented milk RR 0·80 (95 % CI 0·71, 0·89); and cheese RR 0·94 (95 % CI 0·89, 0·995) associated with a reduced risk of stroke		
Soedamah-Muthu et al. (2013)[32]	Milk	Dose–response meta-analysis. Seventeen prospective studies	Modest inverse association (four studies; RR 0·94 per 200 ml/d; 95 % CI 0·89, 0·99)	No association (six studies; RR 0·87; 95 % CI 0·72, 1·05)	No association (six studies; RR 1·00; 95 % CI 0·96, 1·04)	
Soedamah-Muthu et al. (2011)[35]	Total dairy products	Meta-analysis. Four prospective cohorts	No significant association (RR 1·02; 95 % CI 0·93, 1·11)			
Soedamah-Muthu et al. (2011)[35]	Total high-fat dairy products	Meta-analysis. Four prospective cohorts	No significant association (RR 1·04; 95 % CI 0·89, 1·21)			
Soedamah-Muthu et al. (2011)[35]	Total low-fat dairy products	Meta-analysis. Three prospective cohorts	No significant association (RR 0·93; 95 % CI 0·74, 1·17)			
Elwood et al. (2010)[31]	Milk	Systematic review. Meta-analysis of 38 cohort studies. Five case–control retrospective studies		Inverse association (RR 0·79; 95 % CI 0·68, 0·91)		Inverse association (RR 0·79; 95 % CI 0·68, 0·91)
Elwood et al. (2010)[31]	Cheese	Systematic review. Six cohort studies used a fixed-effects model and weighted studies appropriately	Inverse association (RR 0·90; 95 % CI 0·79, 1·03)			

Table 1. *Continued*

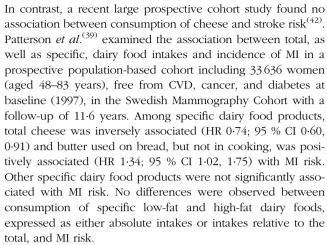| Reference	Dairy food	Methodology	Overall CVD	Stroke	CHD	IHD
Elwood *et al.* (2010)[31]	Butter	Systematic review. Five cohort studies	Three cohort studies suggest a reduction in vascular disease risk (RR 0·93; 95 % CI 0·84, 1·02) while two cross-sectional studies suggest an increase and another an increase in peripheral artery disease			
Elwood *et al.* (2008)[30]	Milk (milk, whole milk, low-fat milk, high-fat milk), dairy products, dairy Ca	Meta-analysis of 15 studies (11 for heart disease and seven for stroke)		Inverse association (RR 0·79; 95 % CI 0·75, 0·82)		Inverse association (RR 0·83; 95 % CI 0·74, 0·91) for milk; RR 0·84 (95 % CI 0·76, 0·93) for milk/dairy products
German *et al.* (2009)[158]	Dairy products not defined but include milk, cheese and butter	Narrative review. Data from 12 cohorts involving >280 000 subjects	Seven cohorts found no association. Three cohorts reported a positive association. One cohort reported a positive association between CVD and butter, but a negative association with cheese			
German *et al.* (2009)[158]	Cheese	Narrative review. Data from 12 cohorts involving >280 000 subjects	One cohort reported a negative association. Limited evidence indicates cheese is most likely to be associated with a reduced risk of CVD			
German *et al.* (2009)[158]	Two cohorts used dairy foods as a group; two used milk intake; three measured Ca in dairy products; six reported various combinations of dairy products: milk and cheese; milk and butter; butter and cheese or whole milk, skimmed milk, high- and low-fat dairy products	Narrative review. Data from 12 cohorts involving >280 000 subjects	Four found no association. Eight reported inconsistent associations. No consistent evidence that dairy food consumption is associated with a higher risk of CVD			

RR; relative risk; RCT, randomised controlled trial.

found between dairy product consumption and CHD risk, which supports previous findings from Soedamah-Muthu et al.[35].

Butter

There are few studies examining the effects of individual dairy foods such as butter on CVD risk[31]. Butter is rich in milk fat and SFA, which increase blood total and LDL-cholesterol levels and is therefore often associated with an increased risk of CVD[40]. However, studies have shown that milk with lower fat and SFA, and butter have similar effects on blood cholesterol levels[40]. Furthermore, a meta-analysis of data from three cohorts suggested no effect, while two case–control studies suggested an increase in vascular disease, and one case–control indicated an increase in peripheral artery disease from butter intake[31]. More recently Goldbohm et al.[21] reported a slightly increased risk in all-cause and IHD mortality for both butter and dairy fat intake (per 10 g/d; rate ratio mortality 1·04; 95 % CI 1·01, 1·06) in women only. However, Larsson et al.[19] in an analysis of butter intake and the incidence of stroke found no strong association between butter intake and stroke in men. Although there were no associations between butter consumption and the risk of cerebral infarction or subarachnoid haemorrhage, the risk of intracerebral bleeding was slightly increased for men in the highest quintile of butter intake (79 g/d) compared with those in the lowest quintile (RR 1·44; 95 % CI 1·01, 2·07), but the trend in RR with increasing butter intake was not significant ($P = 0.19$)[19]. In a recent cohort study, Sonestedt et al.[41] evaluated the association between butter and cream intake and incidence of CVD in middle-aged Swedish men and women followed for 12 years. When the highest and lowest levels of intake were compared, no association was found between butter or cream intake and incident CVD (HR 0·94; 95 % CI 0·83, 1·07; P for trend = 0·16; and HR 0·93; 95 % CI 0·83, 1·06; P for trend = 0·10, respectively). Overall, the evidence from prospective studies on butter in relation to CVD risk appears conflicting, although the balance of evidence suggests either no effect or a slight detrimental impact on CVD risk; however, additional long-term studies are required to further elucidate associations between butter and CVD risk.

Cheese

The evidence on the effects of cheese consumption and CVD risk is also limited[31]. Elwood et al.[31] showed an estimate of RR from cheese consumption of 0·90 (95 % CI 0·79, 1·03) in a meta-analysis of two prospective cohort studies. The authors found six studies in the literature examining the effects of cheese on CVD risk, but sufficient data were only available in two of these studies. Since then a number of prospective cohort studies have been published. For example, the Netherlands Cohort Study reported no association between cheese intake and IHD mortality[21]. In addition, no significant association between full-fat cheese intake and CVD mortality was observed in a population-based sample of Australian adults followed for 14·4 years[20]. However, another recent study involving 26 445 adults from the Swedish Malmö Diet and Cancer cohort with 12 years of follow-up showed that cheese intake was significantly associated with CVD risk in those with the highest intake[41].

In contrast, a recent large prospective cohort study found no association between consumption of cheese and stroke risk[42]. Patterson et al.[39] examined the association between total, as well as specific, dairy food intakes and incidence of MI in a prospective population-based cohort including 33 636 women (aged 48–83 years), free from CVD, cancer, and diabetes at baseline (1997), in the Swedish Mammography Cohort with a follow-up of 11·6 years. Among specific dairy food products, total cheese was inversely associated (HR 0·74; 95 % CI 0·60, 0·91) and butter used on bread, but not in cooking, was positively associated (HR 1·34; 95 % CI 1·02, 1·75) with MI risk. Other specific dairy food products were not significantly associated with MI risk. No differences were observed between consumption of specific low-fat and high-fat dairy foods, expressed as either absolute intakes or intakes relative to the total, and MI risk.

Recently, Hjerpsted & Tholstrup[43] published a review of the evidence on cheese and CVD risk. They reported that four prospective studies showed no association of cheese intake with CVD, two showed a decreased risk and one an increased risk. Another study showed no association in men, but a decreased risk in women. They concluded that, when the prospective data were considered alongside the lack of deleterious effects on blood cholesterol seen in the studies, overall, cheese may not increase the risk of CVD although more work is needed to understand the mechanisms at work.

Conclusions

The majority of prospective studies or meta-analyses examining the relationship between milk and dairy products, except butter consumption and risk of CVD and stroke, most, but not all showed either no relationship or inverse associations (Table 1). A limited number of studies examined the association between the intake of total high-fat or total low-fat dairy products and the risk of CHD or stroke. Therefore, additional studies of this nature are needed, as well as studies examining the effects of individual dairy products, particularly cheese and butter, on CVD risk.

Effect of milk and dairy products on risk of type 2 diabetes mellitus and the metabolic syndrome

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) accounts for at least 90 % of all diabetes cases and its prevalence has been increasing at an alarming rate in many countries. A growing body of evidence suggests that milk and dairy product consumption is associated with a reduced risk of T2DM, possibly due to the beneficial effects of dairy products on obesity and the MetS, two important risk factors for T2DM, as well as the beneficial role of certain dairy components such as protein, Ca, vitamin D, dairy fat and specifically trans-palmitoleic acid[44,45].

Seven meta-analyses of prospective cohort studies on dairy products and T2DM were identified (Table 2). In the meta-analysis by Tong et al.[46] the highest dairy product consumption, compared with the lowest category, showed a significantly reduced risk of T2DM by 14 % (pooled RR 0·86; 95 % CI 0·79, 0·92).

Table 2. Summary of epidemiological studies on milk and dairy product intake and risk of type 2 diabetes mellitus (T2DM)

Study type and reference	Subjects (n)	Population characteristics Sex	Age (years)	Other	Dairy food	Main outcomes
Prospective						
Choi et al. (2005)[159]	41 254	M	40–75	Healthcare professionals without diabetes, CVD or cancer	Total dairy product intake, LFD and HFD	Consuming ≥2·9 portions/d resulted in a lower risk of T2DM compared with ≤0·9 portions/d
Liu et al. (2006)[60]	37 183	F	55	Without diabetes, CVD or cancer	Total dairy product intake, LFD and HFD	Consuming ≥2·9 portions/d resulted in a lower risk of T2DM compared with ≤0·85 portions/d
Elwood et al. (2007)[61]	2375	M	45–59	Without diabetes	Dairy product and/or milk intake	No correlation between milk intake and T2DM. OR for metabolic syndrome lower in subjects who consumed ≥1 cup or more of milk or other dairy products (adjusted OR for milk 0·38; 95 % CI 0·18, 0·78)
Kirii et al. (2009)[160]	59 796	M/F	45–74	Japanese without CVD, chronic lung disease or chronic kidney disease	Total dairy product, Ca and vitamin D intake	Ca did not reduce odds of T2DM. Intake of Ca and vitamin D reduced risk for T2DM. Dairy product intake was associated with lower odds of T2DM in women
Fumeron et al. (2011)[68]	3435	M/F	30–65	–	Total dairy product intake (milk, cheese and other)	Intake of other dairy products (not cheese) and total Ca was inversely associated with incidence of T2DM
Margolis et al. (2011)[161]	82 076	F	50–79	Postmenopausal women	Total dairy product intake, LFD and HFD	Consumption of >1·5 regular dairy product portions/d reduced the risk of T2DM, especially among women with the highest BMI
Grantham et al. (2012)[162]	5582	M/F	25–88	Adults ≥25 years, 209 with and 5373 without diabetes	Total dairy products, total milk, low-fat milk, high-fat milk, yoghurt, cheese	Highest v. lowest total dairy product intake associated with a significantly reduced risk of diabetes in men (OR 0·53; 95 % CI 0·29, 0·96). Similar trend for women but not significant
Sluijs et al. (2012)[50]	16 835	M/F	Mean 51–53	Adults from eight European Union countries in EPIC-InterAct study	Total dairy products, milk, yoghurt, cheese and combined fermented foods	Highest v. lowest total dairy product intake not associated with T2DM but cheese had inverse association with T2DM (HR 0·88; 95 % CI 0·76, 1·02; P for trend = 0·01). Higher intake of all fermented foods (cheese, yoghurt and thick fermented milk) inversely associated with T2DM (HR 0·88; 95 % CI 0·78, 0·99; P for trend = 0·02)
Soedamah-Muthu et al. (2013)[32]	4526	M/F	56	Mostly Caucasian	Total dairy product intake, LFD and HFD	Inconsistent correlation with T2DM
Stuijk et al. (2013)[163]	5953	M/F	30–60	Danish without diabetes or CVD	LFD, HFD, milk and milk products, cheese and FMD	No association between any total dairy products or any of the dairy product subgroups with T2DM
Louie et al. (2013)[69]	1802	M/F	≥49	Australian	Total dairy product intake, LFD and RFD	In obese subjects, high intake of regular-fat dairy foods associated with reduced risk of T2DM; OR 0·37 (95 % CI 0·16, 0·88), not after adjustment for additional confounders. No association between total dairy product consumption and risk of T2DM
Zong et al. (2014)[164]	2091	M/F	50–70	Chinese, 6 years follow-up	Total dairy products including mainly milk, yoghurt, ice cream and milk powder	Compared with non-consumers, the RR of T2DM in those having 0·5–1 serving/d and >1 serving/d were 0·70 (95 % CI 0·55, 0·88) and 0·65 (95 % CI 0·49, 0·85), respectively, after multivariate adjustment
Diaz-Lopez et al. (2016)[51]	3454	M/F	55–80	Spanish Mediterranean, 4·1 years median follow-up	Total low-fat, whole-fat, and subgroups: milk, yoghurt, cheeses, fermented dairy products, concentrated full fat, and processed dairy products	Total dairy products inversely associated with T2DM risk: RR 0·68 (95 % CI 0·47, 0·98), mainly attributed to low-fat dairy; RR 0·65 (95 % CI 0·45, 0·94) for low-fat dairy products and 0·67 (95 % CI 0·46, 0·95) for low-fat milk

Table 2. *Continued*

Study type and reference	Subjects (*n*)	Population characteristics		Other	Dairy food	Main outcomes
		Sex	Age (years)			
						Total yoghurt consumption was associated with a lower T2DM risk (HR 0·60; 95 % CI 0·42, 0·86; *P* for trend = 0·002)
Meta-analyses						
Pittas *et al.* (2007)[165]	–	–	–	18 Cross-sectional studies, eight prospective but not all used for dairy foods	Total dairy product, Ca and vitamin D intake	High Ca doses (661–1200 mg/d) and vitamin D reduced odds of T2DM compared with low doses (219–600 mg/d) Consumption of three to five dairy food portions/d reduced odds of T2DM compared with 1·5 dairy portions/d
Elwood *et al.* (2008)[30]	–	–	–	Four prospective studies, 120 263 subjects, 4851 cases	Total dairy product intake	Reduced risk of T2DM in individuals with the highest compared with the lowest dairy product intake (RR 0·92; 95 % CI 0·86, 0·97)
Tong *et al.* (2011)[46]	–	–	–	Seven prospective studies, 328 029 subjects, 13 078 cases	Total dairy product intake, LFD and HFD consumption	Dairy product consumption reduced risk of T2DM The effect was higher with LFD (RR 0·82; 95 % CI 0·74, 0·90)
Aune *et al.* (2013)[47]	–	–	–	17 Prospective studies, 526 482 subjects, 30 999 cases	Total dairy product intake, HFD, LFD, milk, cheese, yoghurt and other dairy foods	Significant inverse association between total dairy product intake (RR 0·93; CI 0·87, 0·99) with ≥400 g/d, LFD (RR 0·91; CI 0·86, 0·96) with ≥200 g/d and cheese (RR 0·92; CI 0·86, 0·99) with ≥50 g/d, and RR of T2DM
Gao *et al.* (2013)[166]	–	–	–	13 Studies, 457 893 subjects, 27 095 cases	Total dairy product intake, HFD, LFD, milk, cheese, yoghurt and other dairy foods	Inverse association between T2DM and total dairy products (RR 0·95; 95 % CI 0·92, 0·98) per 200 g/d, LFD (RR 0·88; 95 % CI 0·84, 0·93) per 200 g/d, cheese (RR 0·80; 95 % CI 0·69, 0·93) per 30 g/d and yoghurt (RR 0·91; 95 % CI 0·82, 1·00) per 50 g/d
Chen *et al.* (2014)[48]	–	–	–	14 Prospective studies, 439 790 subjects, 35 863 T2DM cases		Yoghurt associated with reduced risk of T2DM (RR 0·82; 95 % CI 0·70, 0·96) per one serving/d whereas other dairy foods and consumption of total dairy products were not appreciably associated
Gijsbers *et al.* (2016)[49]	–	–	–	22 Prospective studies, total of 579 832 subjects including 43 118 T2DM cases	Total dairy products, LFD, yoghurt and ice cream	Per 200 g/d total dairy products and LFD inversely associated with T2DM risk: RR 0·97 (95 % CI 0·95, 1·00) and RR 0·96 (95 % CI 0·92, 1·00), respectively. Total yoghurt consumption was associated with a lower T2DM risk at 80 *v.* 0 g/d: RR 0·86 (95 % CI 0·83, 0·90)

M, male; LFD, low-fat dairy products; HFD, high-fat dairy products; F, female; EPIC-InterAct, European Prospective Investigation into Cancer and Nutritional Study; FMD, fermented dairy products; HR, hazard ratio; RR, relative risk.

A significant inverse association was also observed for T2DM following low-fat dairy product and yoghurt consumption. However, high-fat dairy products and whole (regular-fat) milk were not found to be associated with T2DM. A dose–response analysis showed a 6 % reduced risk of T2DM with each additional daily serving of total dairy products (RR 0·94; 95 % CI 0·92, 0·97). Similarly, each additional serving of low-fat dairy products was associated with a 10 % reduction in T2DM risk (RR 0·90; 95 % CI 0·86, 0·97). In a systematic review and meta-analysis involving five cohort studies with 184 454 participants, the RR for T2DM was estimated to be 15 % lower in individuals who had a high milk intake[31].

More recently, a systematic review and dose–response meta-analysis reported that a high intake of total dairy products was associated with a significant decrease in risk of T2DM (RR 0·89; 95 % CI 0·82, 0·96) and this reduction in risk was 7 % less for every 400 g total dairy product consumed per d[47]. In addition, significant inverse associations were also found for low-fat dairy products (RR 0·83; 95 % CI 0·76, 0·90), low-fat or skimmed milk (RR 0·82; 95 % CI 0·82, 0·69), cheese (RR 0·91; 95 % CI 0·84, 0·98) and yoghurt (RR 0·86; 95 % CI 0·75, 0·98), but not for high-fat dairy or total milk when high v. low consumption was compared. The dose–response analysis also revealed that for 200 g low-fat dairy products (RR 0·91; 95 % CI 0·86, 0·96), low-fat or skimmed milk (RR 0·89; 95 % CI 0·84, 0·95) or yoghurt (RR 0·78; 95 % CI 0·60, 1·02) per d the risk of T2DM was 9, 11 and 22 % lower, respectively. The consumption of 50 g of cheese (RR 0·92; 95 % CI 0·86, 0·99) per d was also associated with an 8 % lower risk of T2DM[47]. The meta-analysis of fourteen cohort studies by Chen et al.[48] also showed that yoghurt was associated with reduced risk of T2DM (RR 0·82, 95 % CI 0·70, 0·96 per one serving/d) whereas other dairy foods and consumption of total dairy products were not appreciably associated. The very recent meta-analysis of Gijsbers et al.[49] involved twenty-two prospective studies with a total of 579 832 subjects including 43 118 T2DM cases. Total dairy products and low-fat dairy products were both inversely associated with T2DM risk (RR 0·97 per 200 g/d; 95 % CI 0·95, 1·00; RR 0·96 per 200 g/d; 95 % CI 0·92, 1·00, respectively). They showed a stronger and non-linear inverse association for yoghurt intake (80 v. 0 g/d RR 0·86; 95 % CI 0·83, 0·90), suggesting that yoghurt in particular may have value for reducing the risk of T2DM.

Recent studies support the findings from these meta-analyses. Intake of total dairy products was not found to be associated with T2DM in a nested case–cohort study in a random sub-cohort (n 16 154) and incident T2DM cases (n 12 403) from the European Prospective Investigation into Cancer and Nutritional Study (EPIC)-InterAct in the highest v. lowest quintile of consumption[50]. However, it was reported that cheese intake tended to have an inverse association with T2DM (HR 0·88; 95 % CI 0·76, 1·02; P for trend = 0·01) and a higher intake of all fermented foods (cheese, yoghurt and thick fermented milk) was also inversely associated with T2DM (HR 0·88; 95 % CI 0·78, 0·99; P for trend = 0·02) after adjustment when comparing extreme quintiles[50]. Diaz-Lopez et al.[51] also showed that total yoghurt consumption was associated with a lower T2DM risk (HR 0·60; 95 % CI 0·42, 0·86; P for trend = 0·002).

Overall, there is a strong and relatively consistent body of evidence suggesting that dairy products may be associated with a reduced risk of T2DM, which is likely to occur in a dose-dependent manner. In addition, evidence on regular-fat dairy products suggests no association with T2DM or a beneficial impact, and the role of fermented dairy products such as cheese and yoghurt appears to be particularly beneficial.

The metabolic syndrome

The concurrent presence of certain CVD risk factors, notably insulin resistance, abdominal obesity, hypertension, elevated fasting blood glucose, elevated TAG and low HDL-cholesterol, is recognised as the MetS. This cluster of disorders has been associated with a 2-fold greater risk of CVD events over 5–10 years[52]. In addition, patients with the MetS are five times more likely to develop T2DM compared with patients that do not[52]. The prevalence of the MetS in adults in developed countries is 22–39 % and varies depending on definition used and ethnicity[53–55]. Recommendations for preventing and managing the MetS include reducing obesity, increasing physical activity and dietary change[56].

The findings of selected epidemiological studies on milk and dairy product intake in relation to the MetS are shown in Table 3. In a systematic review of most of the observational studies in Table 3, Crichton et al.[57] reported that dairy product or milk intake was inversely associated with the prevalence of the MetS in five[58–62] out of ten cross-sectional studies. Furthermore, individuals with the MetS were more likely to consume high-fat dairy products compared with low-fat dairy products in one cross-sectional study of 1181 adults[58]. In the three prospective studies examined, two found inverse associations between incidence of the MetS and dairy product consumption in overweight[63] and normal-weight adults[64]. There were three studies that did not find any association between dairy product intake and MetS prevalence[65,66] or incidence[67]. The authors of the systematic review concluded that although the majority of studies showed beneficial effects of dairy product intake on the risk of having the MetS, methodological differences, potential biases and other limitations in the studies prevented conclusions from being drawn[57].

In a French prospective study with a 9-year follow-up, Fumeron et al.[68] reported that dairy product (expect cheese) consumption and dietary Ca density were inversely associated with incident MetS and T2DM and all parameters were associated with lower diastolic blood pressure and TAG levels. More recently, Louie et al.[69] reported that the HR of developing the MetS was 0·41 (95 % CI 0·23, 0·71) for the highest quartile of regular-fat dairy product intake v. the lowest dairy product intake in 1802 Australian adults. Shin et al.[70] reported an inverse association between total dairy product intake (>7 times/week) and the MetS (HR 0·75; 95 % CI 0·64, 0·88), and milk intake (>7 times/week) and the MetS (HR 0·79; 95 % CI 0·67, 0·92) in a prospective study of 7240 Korean adults. Few studies have investigated the effects of butter consumption on the MetS. One study investigated the effects of butter from mountain-grazed dairy cows on risk markers of the MetS compared with conventional Danish butter[71]. The study was a double-blind, randomised, 12-week, parallel intervention in thirty-eight healthy subjects. It was reported that there were no significant differences in blood lipids, lipoproteins, high-sensitivity

Table 3. Summary of epidemiological studies on milk and dairy product intake and the metabolic syndrome (MetS)

Type of study and reference	Subjects (n)	Sex	Age (years)	Other	Dairy food	Main outcomes
Prospective						
Lutsey et al. (2008)[63]	9514	M/F	45–64	Enrolled in the Atherosclerosis Risk in Communities study	Total dairy product intake	Dairy product intake inversely associated with the MetS (HR 0·87; 95 % CI 0·77, 0·98). Individual dairy foods not associated with the MetS
Fumeron et al. (2011)[68]	3435	M/F	30–65	French without diabetes at baseline	Total dairy product intake (milk, cheese and other)	Intake of other dairy products (not cheese) and total Ca was inversely associated with incidence of IRS and fasting hyperglycaemia
Louie et al. (2013)[69]	1802	M/F	≥49	Australian	Total dairy product intake, LFD and RFD	The highest quartile had a 59 % lower risk of the MetS (OR 0·41; CI 0·23, 0·71; P for trend = 0·004) compared with the lowest quartile of RFD intake
Shin et al. (2013)[70]	7240	M/F	40–69	Korean without the MetS at baseline	Milk, cheese and yoghurt intake	Total dairy product intake (>7 times/week) was inversely associated with the risk of the MetS (HR 0·75; 95 % CI 0·64, 0·88; P for trend <0·001). Milk intake (>7 times/week) was inversely associated with the risk of the MetS (HR 0·79; 95 % CI 0·67, 0·92; P for trend = 0·002) when compared with no milk intake/week
Cross-sectional						
Yoo et al. (2004)[58]	1181	M/F	19–38	25 % African American and 75 % whites	HFD and LFD intake	Adults with the MetS consumed significantly less LFD (0·52 servings/d) and more HFD (0·95 servings/d) than those with no risk factors (0·73 servings/d) (P < 0·05)
Azadbakht et al. (2005)[59]	827	M/F	18–74	Tehranian	Milk, yoghurt and cheese intakes	Dairy product intake was inversely associated with the MetS (OR 0·82; 95 % CI 0·63, 0·99)
Liu et al. (2006)[60]	37 183	W	–	Without diabetes, CVD or cancer at baseline	Total dairy product intake, HFD, LFD, total milk intakes	Dairy product intake was inversely associated with the MetS: total dairy products (OR 0·66; 95 % CI 0·55, 0·80), HFD (OR 0·71; 95 % CI 0·58, 0·87), LFD (OR 0·78; 95 % CI 0·64, 0·95) and total milk (OR 0·85; 95 % CI 0·71, 1·02)
Elwood et al. (2007)[61]	2375	M	45–59	Caerphilly cohort without diabetes at baseline	Total dairy product and milk intakes	At baseline milk intake was inversely associated with the MetS (RR 0·38; 95 % CI 0·18, 0·78). The highest quartile (highest energy from dairy products) was inversely associated with the MetS (OR 0·40; 95 % CI 0·20, 0·79)
Snijder et al. (2007)[65]	2064	M/W	50–75	Dutch population from the Hoorn study	Total dairy product intake, milk, yoghurt, cheese and dairy dessert intakes	No association with dairy product intake and the MetS
Ruidavets et al. (2007)[62]	912	M	45–64	French population	Total dairy product (milk and cheese) intakes	Dairy product intake was inversely associated with the MetS (OR 0·67; 95 % CI 0·47, 0·94)
Beydoun et al. (2008)[72]	4519	M/F	≥18	US population	Dairy products (milk, cheese, yoghurt)	Yoghurt intake was inversely associated with the MetS (OR 0·40; 95 % CI 0·18, 0·89)
Shin et al. (2009)[66]	7081	M	≥30	Korean population	Total dairy product intake	No association between dairy product intake and the MetS
Mennen et al. (2000)[167]	4976	M/F	30–64	French population		Dairy product intake was inversely associated with the MetS in men (OR 0·63; 95 % CI 0·40, 0·99)
Hong et al. (2012)[168]	406	M/F	22–78	Korean population	Total dairy product intake	Dairy product intake was associated with reduced odds of having the MetS (OR 0·46; 95 % CI 0·22, 0·95; P for trend = 0·025)
Kim (2013)[169]	4862	M/F	≥19	Korean with and without the MetS	Milk, cheese and yoghurt intake	The prevalence of the MetS was significantly lower in subjects with higher milk or yoghurt consumption (P < 0·0001). Lower odds of the MetS with high milk (OR 0·71; 95 % CI 0·55, 0·93; P for trend = 0·0066) or yoghurt (OR 0·71; 95 % CI 0·48, 1·05; P for trend = 0·0067)
Drehmer et al. (2016)[170]	15 105	M/F	35–74	Brazilian civil servants from six cities	Total dairy product, HFD, LFD and a range of dairy foods. Butter included	Increased total dairy product intake, especially of full-fat dairy products, associated with reduced risk of the MetS in middle-aged and older adults. OR for highest total dairy product intake: 0·75 (95 % CI 0·61, 0·92, P for trend = 0·002). Data suggest that fat in dairy products may explain the potential protective effect of dairy product intake

M, male; F, female; HR, hazard ratio; LFD, low-fat dairy products; RFD, regular-fat dairy products; IRS, insulin resistance syndrome; HFD, high-fat dairy products; RR, relative risk.

C-reactive protein, insulin, glucose or glucose tolerance between butters. The authors suggested that the lack of effects on blood lipids and inflammation may indicate that dairy products from mountain pasture-grazing cows are not healthier than products from high-input conventional systems. Although some studies suggest a possible beneficial effect of milk and dairy product consumption in relation to individual components of the MetS, there is a need for additional studies to determine the relationship between milk and dairy product intake and risk of the MetS[71].

A study performed in an ethnic diverse US population revealed that the OR for MetS per one additional daily serving of yoghurt was 0·40 (95 % CI 0·18, 0·89), whereas the opposite was found for cheese (OR 1·16; 95 % CI 1·04, 1·29) in a cohort of 4519 men and women[72]. This beneficial association of yoghurt consumption was confirmed in children living in the USA using data from the National Health and Nutrition Examination Survey (NHANES) cohort (5124 children aged 2–18 years)[73]. Frequent yoghurt consumption (once per week) was associated with significantly lower metabolic profiles, including plasma insulin and markers of insulin resistance[73]. In the first 6 years of follow-up of the SUN cohort it was reported that frequent consumption of yoghurt (>7 servings/week) compared with low consumption (two servings/week) only showed a non-significant inverse association with the MetS (OR 0·84; 95 % CI 0·60, 1·18). Yet in those with the highest category of total yoghurt consumption combined with a high fruit consumption (above the median ≥264·5 g/d) a significantly lower risk of developing the MetS was observed (OR 0·61; 95 % CI 0·38, 0·99) compared with those in the lowest category of total yoghurt and fruit consumption below the study median[74].

Conclusions

The majority of studies to date suggest a beneficial role of dairy product consumption in relation to risk of the MetS and T2DM. Further research is needed in order to better understand the role of regular-fat and specific types of dairy products (fermented products in particular) on the incidence of T2DM and components of the MetS. There is a need for RCT to examine the effects and mechanisms of long-term dairy product consumption on cardiometabolic risk factors, particularly in at-risk populations such as those with T2DM/MetS.

Effect of milk and dairy products on markers of cardiometabolic disease risk

The available evidence on the relationship between milk and dairy product consumption and individual markers of disease risk such as elevated plasma lipids, glucose and inflammatory markers, insulin resistance, hypertension and increased body weight and composition is reviewed.

Dairy products and blood lipids

Dairy fat consists of large numbers of fatty acids and other lipid molecules that have different effects on human health. The fat content of 'whole' or 'full-fat' milk is approximately 3·3 g fat/100 g, which consists primarily of TAG (97–98 % of total lipids by weight). The TAG are composed of fatty acids of differing lengths (4–24 carbon atoms) and levels of saturation. Whole milk contains approximately 2·2 g of SFA/100 g, 0·8 g/100 g of oleic acid (18 : 1,cis-9), the main MUFA, 0·2 g/100 g of PUFA and approximately 0·1 g/100 g of ruminant-derived TFA. The relationship between milk fat consumption and health is complex and numerous intervention trials, using a variety of fat sources, have investigated the impact of dietary fat composition on the blood lipid (including on cholesterol and TAG) concentrations in human subjects.

There is consistent evidence that consumption of dietary SFA increases serum total and LDL-cholesterol concentrations, a robust indicator of CHD risk[75]. In addition, evidence from a number of prospective studies suggests increased serum total cholesterol in high dairy product compared with low dairy product consumers[24,27]. A positive association between intake of SFA from dairy products and total cholesterol has been shown using evidence from studies carried out throughout the European Union[76]. However, individual SFA have been shown to have different effects on blood lipids, for example lauric (12 : 0), myristic (14 : 0) and palmitic (16 : 0) acids are associated with elevated serum levels of LDL-cholesterol, whereas stearic acid (18 : 0), which is poorly absorbed, has limited effects on LDL-cholesterol[5]. Given that much of the 12 : 0, 14 : 0 and 16 : 0 in the human diet is derived from milk fat, the consumption of milk and dairy foods would be expected to have adverse effects on serum LDL-cholesterol concentrations. There is, however, some doubt that LDL-cholesterol alone, or models including LDL-cholesterol are optimal predictors of CVD risk[77] and perhaps especially for effects of dairy foods the potential value of assessing LDL particle size/density and number needs further evaluation[77,78].

However, in addition to an LDL-cholesterol-raising effect, SFA concomitantly increase anti-atherogenic HDL-cholesterol concentrations, which suggest that the effects of most SFA on blood lipids are atherogenically neutral when based on the total cholesterol:HDL-cholesterol ratio[5,79,80]. However, there is no current consensus on this relationship, as despite extensive evidence that low HDL-cholesterol is a strong marker of CVD risk[81] it has been suggested that serum concentrations of HDL-cholesterol may not reflect HDL functionality and its capacity to reduce risk[82]. This is mainly related to the evidence that whilst blood HDL-cholesterol concentrations have been shown to be inversely associated with CHD risk, dietary interventions that raise HDL-cholesterol do not result in reduced CHD risk[83]. It has been proposed that an assessment of HDL-cholesterol efflux capacity, a measure of the ability of HDL to remove cholesterol from lipid-rich macrophages, may provide more valuable information on HDL function and may be a useful target for therapeutic intervention[83].

It is now becoming clearer that the effects of reducing dietary SFA are best interpreted by an understanding of which macronutrients replace them. Reduced CVD risk has been associated with replacement of SFA with PUFA[80,84,85] and MUFA[86] although replacement with carbohydrate is associated with no improvement or an increase in CVD risk[80]. This has raised the question of whether replacing a proportion of SFA in dairy fat with MUFA and/or PUFA will lead to reduced CVD risk. The very few RCT that have examined this were reviewed

by Livingstone *et al.*[87] who concluded that whilst based on cholesterol changes, there were indications of reduced CVD risk from consumption of milk and dairy products with modified fatty acid composition, compared with those of normal milk fat composition, although the evidence available was weak and inadequate. A new RCT (RESET; ClinicalTrials.gov NCT02089035)[88] is investigating this in depth and preliminary results from a recent meta-analysis of three prospective studies indicated that whilst dairy fat was not significantly associated with CVD, models which estimated the effect of replacing 5 % of energy from dairy fat with vegetable fat predicted a 10 % reduction in CVD risk[89]. The dairy foods that supplied the fat were not specified and data on this are needed to more fully understand this outcome.

In contrast to the results of studies focused on fatty acids, Kai *et al.*[90] reported an inverse association between intake of low-fat dairy products with LDL-cholesterol concentration. Similarly, a number of intervention studies, which specifically investigated the effects of milk and other dairy fats, did not show significantly increased LDL-cholesterol[91–97]. Furthermore, there is evidence that fermented milk products are hypocholesterolaemic relative to non-fermented equivalents[93,98]. In a meta-analysis of six relatively short-term studies it was concluded that the consumption of fermented yoghurt products produced a 4 and 5 % decrease in total and LDL-cholesterol[98]. Biong *et al.*[93] observed significantly lower LDL-cholesterol ($P = 0.03$), differences of 0·15–0·26 mmol/l following the consumption of a cheese *v.* a butter-enriched standard diet for 3 weeks. More recently Maki *et al.*[96], showed that there was no significant differences in fasting lipoprotein concentrations in sixty-two participants with prehypertension or stage 1 hypertension after 5 weeks of consuming one serving/d of low-fat dairy products compared with non-dairy products. It has also been observed that high dairy product consumption (four servings/d) did not significantly alter blood lipid and lipoprotein responses compared with low dairy product consumption (two servings/d) in twenty-three healthy participants over a 6-month period[97].

A recent systematic review and meta-analysis of RCT compared blood lipid responses from butter and hard cheese and showed that the cheese lowered LDL-cholesterol and to a lesser extent HDL-cholesterol relative to butter, despite consumption of the same amount of dairy fat[99]. There are several proposed mechanisms for the so-called matrix effect of cheese. Cheese is a rich source of Ca and there are indications that the Ca forms insoluble soaps with fatty acids in the gut leading to less fat being absorbed, as indicated by increased faecal fat excretion in some[100] but not all[101] studies. Lorenzen & Astrup[100] also reported an increased faecal excretion of bile acids, due possibly to Ca binding, thus reducing the entero-hepatic recycling of bile acids resulting in a movement of plasma LDL-cholesterol into the liver to support further bile acid synthesis. There is also evidence that dairy products with at least a proportion of the milk fat globule membranes (MFGM) intact will lead to less fat being absorbed[102]. A recent study compared 40 g of milk fat consumed as either whipping cream with MFGM largely intact or butter milk with little MFGM and found that the butter milk produced substantial increases in plasma total and LDL-cholesterol whereas the whipping cream showed no significant changes[102]. These various food matrix effects need to be factored into the estimate of cardiometabolic disease risk associated with individual dairy products. This highlights the importance of understanding the food vehicle and matrix, which requires consideration in addition to the overall contents. So far, only a few cheese types have been investigated and there remains uncertainty about the mechanisms which reduce fat absorption, although Ca appears to play a major role. It is of note that Soerensen *et al.*[103] showed that milk and cheese with the same Ca content both gave significantly smaller LDL-cholesterol responses than butter with a low Ca content.

A recent study comparing blood lipid responses from butter and olive oil (both at 4·5 % energy intake) is of interest[104]. Butter increased total cholesterol and LDL-cholesterol more than olive oil ($P < 0.05$) and more than the run-in period ($P < 0.005$ and $P < 0.05$, respectively) and increased HDL-cholesterol relative to the run-in period ($P < 0.05$). No differences between butter and olive oil were seen for TAG, high-sensitivity C-reactive protein, insulin and glucose concentrations. This whole area needs more detailed investigation since it also has substantial implications for long-term energy and Ca balance. Research to date is suggestive that the matrix affect is mediated primarily through a reduction in absorption of dietary fat and hence SFA by mechanisms such as Ca saponification[100] or protection by MFGM[102]. No direct effects on absorption have been reported and future research should focus on determining the effect that the food matrix has on the magnitude of fatty acid absorption using, for example, stable isotope tracers. This should link to more detailed studies on the chemistry of the resulting faecal fat/fatty acids to confirm or otherwise the presence and structure of Ca soaps and/or Ca bile acid complexes.

The consumption of dietary TFA has long been suspected of increasing the risk of CHD[105] and a number of epidemiological studies have reinforced this hypothesis[106–108]. The current UK population intakes of TFA are, on average, well below the maximum of 2 % of total energy intake set by the Department of Health[109], at approximately 0·7 % of total energy[7]. Dietary TFA originate principally from industrial partial hydrogenation of edible oils and bacterial hydrogenation of unsaturated fatty acids in the rumen of ruminants. Industrially derived TFA are mainly found in snacks and fast foods whereas ruminant-derived TFA are naturally found in milk and dairy products. Milk and dairy products (mainly butter and cheese) contribute approximately 27 % of total TFA intake in the UK diet[7]. However, the isomer distribution of ruminant (normally mainly *trans*-vaccenic acid; *trans*-18 : 1*n*-7) and industrially (mainly elaidic acid; *trans*-18 : 1*n*-9) produced TFA are different and have been shown to have differential effects on the risk of CHD[110]. In addition, a recent meta-analysis of observational studies showed that industrially produced TFA may be positively associated with CHD (RR 1·21; 95 % CI 0·97, 1·50; $P = 0.09$), whereas ruminant TFA was not (RR 0·92; 95 % CI 0·76, 1·11; $P = 0.36$)[105]. Similar differential effects of ruminant and industrial TFA were reported in the recent meta-analysis of de Souza *et al.*[111]. This study also showed an inverse association between ruminant *trans*-palmitoleic acid (*trans*-16 : 1*n*-7) and T2DM (risk ratio 0·58; 95 % CI 0·46, 0·74) which is in accord

with two earlier studies that reported inverse associations between plasma *trans*-palmitoleic acid concentration and incident T2DM[44,45]. It remains unclear, however, whether *trans*-palmitoleic acid has a specific metabolic function, or whether it is simply a marker of dairy food intake. The findings of a differential effect of industrially and ruminant-derived TFA on CHD and the inverse association between *trans*-palmitoleic acid and T2DM are interesting and additional studies in this area are warranted to further elucidate the role of ruminant TFA in the diet.

Taken together, the current evidence presented in this section suggests that, with the possible exception of 16 : 0, the SFA profile of milk may not be as detrimental for CVD risk as previously thought, based mainly on LDL-cholesterol as the sole indicative predictor of risk. It is, however, becoming clearer that differences exist between dairy foods in their ability to raise blood lipids. The contrast between butter and hard cheese is the clearest example to date.

Dairy proteins and blood lipids

Whilst most studies have examined the impact of dairy fat/fatty acids on blood lipids, it is now evident that milk proteins can also influence blood lipids. The rat study of Tong *et al.*[112] using a high-fat diet showed that whey protein significantly increased HDL-cholesterol although this has not been consistently shown in human studies[113]. Some studies have shown whey protein to have a tendency to reduce plasma TAG[114] and total cholesterol[115] and a meta-analysis on the effect of whey protein on blood lipids would be valuable. A recent study[116] showed that compared with whey protein, casein markedly reduced postprandial TAG (22 (SD 10)% reduction in the 6 h AUC; $P < 0.05$). Similar effects were seen for plasma chylomicrons (apoB-48; $P < 0.05$). The authors concluded that in healthy overweight men, casein has specific physical interactions with fat that affect postprandial TAG, leading to the formation of fewer chylomicrons or an increase in chylomicron clearance. It is clear that milk proteins can have important influences of circulating lipids and more work in this area is needed.

Effect of milk and dairy products on blood pressure and arterial stiffness

Hypertension defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg, is one of the leading risk factors for stroke, CHD, heart failure and end-stage renal disease[117]. Diet is one of the most important factors that influence blood pressure[118]. The Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that a diet of reduced total and SFA content and high in low-fat dairy products, and rich in fruit and vegetables significantly lowered blood pressure in normotensive and hypertensive individuals. In addition, the magnitude of blood pressure reduction was of greater magnitude after the diet rich in low-fat dairy products compared with the fruit and vegetable-rich diet, which omitted dairy products altogether[119]. The findings from

cross-sectional and prospective observational studies have shown an inverse association between consumption of dairy products, particularly low-fat varieties, and risk of hypertension[64,65,120–126]. The recent results from the Framingham Heart Study Offspring Cohort (n 2636) also showed benefit from low/reduced fat dairy products[127]. High intakes of total dairy products, total low-fat/fat-free dairy products, low-fat/skimmed milk and yoghurt were associated with lower annualised increments in SBP and a lower overall risk of hypertension. Unlike for most other dairy products, the inverse association with hypertension risk seen with yoghurt was not diminished as follow-up time increased. For yoghurt, each additional serving was associated with a 6 % reduced risk of hypertension (HR 0·94; 95 % CI 0·90, 0·99)[127].

A recent meta-analysis by Soedamah-Muthu *et al.*[125], which included nine prospective cohort studies with a total of 57 256 participants and 15 367 hypertension cases, confirmed these relationships. Specifically they reported that total dairy products (nine studies; consumption range about 100–700 g/d), low-fat dairy products (six studies; about 100–500 g/d) and milk (seven studies; about 100–500 g/d) were inversely and linearly associated with a lower risk of hypertension. Per 200 g/d the pooled RR were 0·97 (95 % CI 0·95, 0·99) for total dairy products, 0·96 (95 % CI 0·93, 0·99) for low-fat dairy, and 0·96 (95 % CI 0·94, 0·98) for milk. High-fat dairy products (six studies), total fermented dairy products (four studies), yoghurt (five studies) and cheese (eight studies) were not significantly associated with hypertension. Soedamah-Muthu *et al.*[125] concluded that the results indicate that low-fat dairy products and milk could contribute to the prevention of hypertension, although further confirmation is needed from RCT. A few RCT have examined the effects of dairy products on blood pressure[96,123,128]. Furthermore, a cross-over RCT by van Meijl & Mensink[123] in thirty-five healthy overweight and obese men and women indicated that daily consumption of low-fat dairy products compared with carbohydrate-rich products for 8 weeks significantly reduced SBP by 2·9 mmHg ($P = 0.027$). However, another study[96] observed no significant effects of consuming low-fat dairy products, compared with low-fat non-dairy products, on blood pressure in sixty-two men and women with prehypertension or stage 1 hypertension.

In addition to the impact on blood pressure, the effect of these foods on other, more novel, markers of vascular health is becoming increasingly relevant. Increased central arterial stiffening is a feature of the ageing process and the consequence of many diseases such as diabetes, atherosclerosis and chronic renal failure. Arterial stiffening is also a marker for increased CVD risk, including MI[129], heart failure[130], total mortality[131], stroke[132] and renal disease[133]. Arterial stiffness is measured by pulse wave velocity and the augmentation index, both of which are predictive of heart attacks and stroke[134] and all-cause mortality[135]. Pulse wave velocity measures the speed of propagation of the pressure wave front along the artery, whereas the augmentation index is calculated from the blood pressure wave form and is based on the degree of wave reflection. Significant associations between dairy product intake and arterial pulse wave velocity have been shown in cross-sectional[136] and longitudinal[126] cohort studies. Livingstone *et al.*[126] presented data from the

Caerphilly Prospective Study, based on 2512 men followed up for a mean of 28 years and showed a significant inverse relationship between dairy product intake and augmentation index. The subjects in the highest quartile of dairy product intake (mean 480 g/d), excluding butter, had a 2 % ($P = 0.02$) lower augmentation index compared with subjects with the lowest dairy product intake (mean 154 g/d), whereas across increasing quartiles of butter intake there were significantly higher insulin, TAG and total cholesterol concentrations, and DBP[126]. The mechanisms by which milk and dairy products may reduce blood pressure and arterial stiffness are unclear. However, it is likely that bioactive peptides released during milk protein digestion may be involved in the relationship between dairy product consumption and blood pressure[137,138]. The bioactive peptides inhibit the action of angiotensin I-converting enzyme, thereby reducing blood levels of angiotensin, preventing blood vessel constriction, and modulating endothelial integrity. A recent meta-analysis of RCT on the effect of casein-derived lactotripeptides confirmed that they do reduce SBP and DBP[139]. Ballard et al.[140] showed that consumption of 5 g of whey-derived peptide daily for a 2-week period significantly improved brachial artery flow-mediated dilation response. There is also some evidence that certain peptides from milk proteins modulate the release of vasoconstrictor endothelin-1 by endothelial cells, thus preventing an increase in blood pressure[141]. Furthermore, milk is a complex food, containing a variety of biologically active components such as Ca, K and Mg that may also have an impact on blood pressure and arterial stiffness[142].

Blood glucose and insulin resistance

The epidemiological evidence described above indicates a potential favourable effect of milk and fermented dairy food consumption on insulin resistance and T2DM. The effects of milk and dairy product consumption on glucose and insulin metabolism would be more reliably evaluated in intervention studies than in observational studies and, although such studies are limited, dairy products are often used as part of an SFA-rich diet. In the KANWU study, which used a relatively large sample size (n 162) and study duration (2 × 12 weeks), a diet high in SFA (partly composed of butter fat) resulted in a significant reduction in insulin sensitivity relative to a cis-MUFA-rich diet, but only in those subjects with a total fat intake of <37 % of total energy intake[143]. In contrast, in the PREMIER study, the consumption of a Dietary Approaches to Stop Hypertension (DASH) diet pattern, which is lower in total fat, SFA and cholesterol and higher in fruit and vegetables and low-fat dairy products, resulted in a 51 % improvement in insulin sensitivity relative to the control group following 6 months of intervention[144]. However, just as in the KANWU study, this trial did not specifically examine the effects of dairy products.

The few intervention studies[94,123,128,136,145–148] that have assessed the effects of milk and dairy product consumption on glucose and insulin concentrations to date were included in a recent systematic review and meta-analysis by Benatar et al.[149]. This showed that there was no significant change in fasting blood glucose between high- and low-fat dairy diets

(overall mean change 1·32, 95 % CI 0·19, 2·45 mg/dl; 0·073, 95 % CI 0·011, 0·136 mmol/l). However, insulin sensitivity as assessed by the homeostatic model assessment of insulin resistance (HOMA-IR) was improved by dairy product consumption in two small studies[128,147] with no effect in the larger studies[94,148]. The study of Frid et al.[150] looked specifically at the effect of whey protein (28 g) on blood glucose control after a high-carbohydrate meal in diabetic patients. The whey protein significantly ($P < 0.022$) reduced peak glucose concentration at 60 min post-consumption and the AUC from 0 to 180 min by 21 %. Milk is known to have an insulinotropic effect[151] and it has been shown that this property is most probably related to the branched-chain amino acids in the whey protein fraction and specifically to leucine[152]. The mechanisms by which whey protein exerts its effect are unclear but one possibility is linked to the finding that whey has been shown to result in a much greater stimulation of glucose-dependent insulinotropic polypeptide (GIP) than other food proteins such as fish, gluten and cheese[152]. The GIP response is possibly a key factor in the higher insulin response and the subsequent lowering of serum glucose seen after whey ingestion, at least in healthy subjects. GIP is one of the key gut hormones released after a meal which enhance insulin secretion in addition to that stimulated by glucose. This so-called incretin effect can contribute up to 50–70 % of the total postprandial insulin response[153].

Whilst most of the evidence relates to the insulinotropic effect of milk, a recent study has indicated that dairy foods may also improve insulin sensitivity. In the study of Rideout et al.[97], twenty-three healthy subjects completed a cross-over RCT of 12 months. Participants consumed their habitual diets and were randomly assigned to one of two treatment groups, i.e. a high-dairy product-supplemented group instructed to consume four servings of dairy products/d (from milk/yoghurt) and a low-dairy product group which consisted of just habitual diet that did not include more than two milk or yoghurt servings/d. At the end of the study the high-dairy group had significantly lower plasma insulin and HOMA-IR than the low-dairy product group.

Overall, there is evidence that consumption of milk and dairy products improves blood glucose homeostasis, probably as the result of an insulinotropic effect, with much less information on insulin sensitivity. This topic is extremely important, particularly with the relatively consistent epidemiological evidence of the benefit of milk and dairy product consumption on risk of type 2 diabetes. Further well-designed intervention studies are needed to more fully understand the effects and the mechanisms.

Inflammation

Low-grade systemic inflammation is now regarded as an important component in the development of chronic disorders including atherosclerosis, the MetS, T2DM and CVD[154]. There is therefore interest in determining the influence, if any, that dairy foods have in the development of inflammation. Several cross-sectional studies[155–157] have indicated that dairy food consumption is inversely associated with inflammation. One study[157] reported that plasma C-reactive protein, IL-6 and TNF-α concentrations were, respectively, 29, 9 and 20 % lower

in subjects who consumed >2 servings dairy products/d compared with those consuming ≤1 serving/d. Because of the limitations of cross-sectional analysis, Labonté et al.[154] undertook a systematic review of RCT that examined the relationship between dairy product consumption and biomarkers of inflammation. Only eight studies with overweight or obese subjects were identified. Only one study had inflammatory marker profile as its primary outcome and this showed that dairy food consumption improved pro- and anti-inflammatory biomarker concentrations compared with the low-dairy control diet.

Overall, Labonté et al.[154] concluded that dairy food consumption does not lead to increased inflammatory biomarker concentrations in overweight or obese subjects. However, because only a few studies have been performed and the variations in methodology used, no clear assessments can be made of individual dairy products. More research is needed in this important area.

Conclusions

The data reviewed suggest that milk and certain dairy products are associated with reductions in blood pressure that are clinically relevant, no increase in body weight (in isoenergetic diets) and may not be as detrimental for CVD risk as previously thought, based mainly on LDL-cholesterol. This is because whilst SFA intake is associated with a clinically significant increase in LDL-cholesterol, there is also an increase in HDL-cholesterol which is also of importance although there is increasing doubt as to the interpretation of blood HDL-cholesterol. It is uncertain whether or how consumption of milk and dairy products improves fasting blood glucose and insulin sensitivity and further well-designed intervention studies are needed to resolve this question. Overall, there is an urgent need for well-designed intervention studies with clearly defined primary outcomes to elucidate the effects of milk and individual dairy products on cardiometabolic risk factors.

Overall conclusions

CVD causes more than a quarter of all deaths in the UK and remains the largest cause of death globally. In addition, the prevalence of T2DM is rapidly rising and is a key risk for CVD development. Dietary strategies in many parts of the world to reduce CVD risk include reduction of saturated fat intake. Milk and dairy products are large contributors to dietary saturated fats in many diets and reduction of intake or elimination is often recommended as a strategy for risk reduction. In prospective studies or meta-analyses examining the relationship between milk and dairy product (except butter) consumption and risk of CVD, stroke and overall cardiometabolic disease, most, but not all show either no relationship or inverse associations. A limited number of studies have examined the association between the intake of total high-fat or total low-fat dairy products and the risk of CHD or stroke, but not all studies use the same definition of high/low-fat products which limits interpretation of outcomes.

Milk is a complex food and contains a number of key nutrients and bioactive components, which may be mechanistically responsible for reduction of disease risk. The present review has

evaluated the current evidence of the association between milk and dairy products and risk of CVD, type 2 diabetes and the MetS. The effects of total and individual dairy foods on cardiometabolic disease risk factors have also been reviewed. The evidence suggests that dairy foods are not associated with detrimental and possibly provide a beneficial effect on CVD risk, with more consistent evidence for a negative relationship with T2DM. Effects of dairy foods on CVD risk factors, including plasma lipids, suggest that the predicted hypercholesterolaemic effect of their SFA is not consistently observed with dairy foods (except butter), most particularly with cheese. The potential value of assessing LDL particle size/density and number, and more functional tests of HDL-cholesterol may be relevant as predictors of CVD risk and need to be assessed in relation to SFA, dairy products and cardiometabolic risk. New information on the effects of the food matrix which may restrict fat digestion and hence fatty acid absorption will be important in this regard. More work is needed to understand the mechanisms involved and to assess if the food matrix can be beneficially altered during cheese making or in other dairy processing procedures. There is growing evidence that milk consumption is associated with lower blood pressure, with peptides released from milk proteins during digestion and Ca being the key proposed mechanisms of action. Overall, the lack of a detrimental effect, and some evidence for potential benefit of milk and dairy product consumption, suggests that dietary restriction or exclusion is not likely to be the optimum approach for cardiometabolic disease risk reduction.

Overall, the policy to reduce SFA intake by reducing dairy food consumption to reduce CVD risk is likely to have a limited or possibly negative effect unless what will replace it is considered together with an understanding of food-related factors. There still remain many uncertainties, not least the differential effects of different dairy products and those of differing fat content, although evidence is building of particular benefits associated with fermented dairy products and milk proteins and studies are needed to better understand their mode of action. Focused and suitably designed and powered research studies are needed to provide clearer evidence not only of the mechanisms involved, but how they may be beneficially influenced during milk production and processing. Given the rapid rise in T2DM prevalence, effects on this should have a high priority. Such studies often appear to be expensive, but relative to the current and future costs associated with cardiometabolic disease, they are likely to be good value.
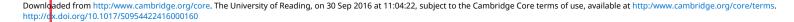
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